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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : CHRISTENSEN, Siegfried, Benjamin, IV [US/US]; 2216 Race Street, Philadelphia, PA 19103 (US).

(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US).

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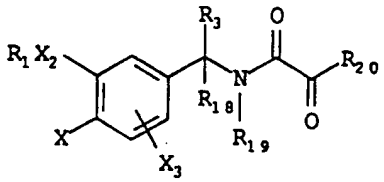

(I)

(57) Abstract

Novel pyrrolidinones of formula (I) are described which inhibit PDE IV and TNF.

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Field of Invention

The present invention relates to novel oxamides, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes:

1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987. The agents currently available (b-adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison et al., Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell sulface receptors, adenylate cyclase is activated which converts Mg^{2+}-ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including:

1) airway sooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the

inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sacroidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with HIV by playing a role in maintaining T lymphocyte activation.

It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

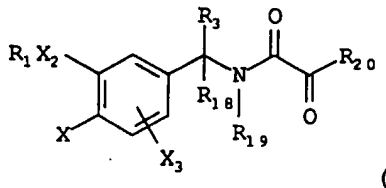
TNF is also associated with yeast and fungal infections. Specifically Candida Albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et

al., Antimicrobial Agents and Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

Summary of the Invention

The compounds of this invention are illustrated by formula (I):



(I)

wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by one or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group, C_{4-6} cycloalkyl containing one or two unsaturated bonds, C_{7-11} polycycloalkyl, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_xOH$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_y$-$R_{11}$, or -$(CR_{14}R_{14})_z$-$R_{10}$;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

Y is O or $S(O)_m$;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -CH_2OR_5, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH{=}CR_9R_9$, -$C{\equiv}CR_9$ or -C(Z)H;

R_4 is independently hydrogen, Br, F, Cl, -NR_5R_{16}, NR_6R_{16}, -NO_2, -C(Z)R_7, -$S(O)_mR_{12}$, -CN, OR_5, -$OC(O)NR_5R_{16}$, (1 or 1-(R_5)-2-imidazolyl), -$C(NR_{16})NR_5R_{16}$, -$C(NR_5)SR_{12}$, -$OC(O)R_5$, -$C(NCN)NR_5R_{16}$, -$C(S)NR_5R_{16}$, -$N(R_{16})C(O)R_{15}$, -$NR_{16}C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are NR_5R_{16} they may together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, -C(O)R_5, -C(O)C(O)R_7, -C(O)NR_5R_{16}, -S(O)$_m R_{12}$, -C(NCN)SR_{12}, -C(NCN)R_{12}, -C(NR_{16})R_{12}, -C(NR_{16})SR_{12}, or -C(NCN)NR_5R_{16};

R_7 is OR_5, -NR_5R_{16}, or R_{12};

R_8 is hydrogen or A;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted arlyoxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydropyranyl), (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cyclo-alkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of these heterocyclic rings is connected at a carbon atom and may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5 or when R_5 and R_{16} are NR_5R_6 they may, together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional hetero atom selected from O, N or S;

R_{18} is hydrogen, F, CN, or C_{1-4} alkyl optionally substituted by one or more fluorines, or R_3 and R_{18} together can form a (=O) keto or cyclopropyl moiety;

R_{19} is hydrogen, -$(CH_2)_m$A, or -$CH_2O(CH_2)_m$A;

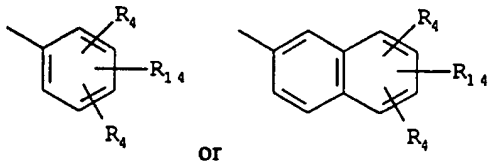
R_{20} is $O(CH_2)_qR_8$, -NR_5OR_5, -$NR_5NR_5R_8$, $NR_5(CH_2)_qR_8$, -$OCH_2NR_5C(O)R_{21}$, -$OCH_2C(O)NR_{22}R_{23}$, -OCH(R_5)OC(O)-, C_{1-4}alkyl, -OCH(R_5)C(O)OC_{1-3}alkyl;

R_{21} is CH_3 or phenyl;

R_{22} is hydrogen, CH_3, CH_2CH_3, or CH_2CH_2OH;

R_{23} is hydrogen, CH_3, CH_2CH_3, CH_2CH_2OH, or CH_2CONH_2;

A is C_{1-6}alkyl, (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl), (4 or 5-thiazolyl), triazolyl or quinolinyl, all of which may be unsubstituted or substituted by one or more R_4 groups; or A is -$(CH_2)_rSR_{12}$; or A is (a) or (b)



or

(a) (b)

where the R_4 and R_{14} groups are at any open position on the naphthyl ring;

Z is O, NR_{12}, NOR_5, NCN, $C(\text{-}CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, $C(\text{-}CN)NO_2$, $C(\text{-}CN)C(O)OR_{12}$ or $C(\text{-}CN)C(O)NR_5R_5$;

m is 0 to 2;

n is 1 to 4;

q is 0 to 1;

r is 1 to 2;

s is 2 to 4;

x is 2 to 6;

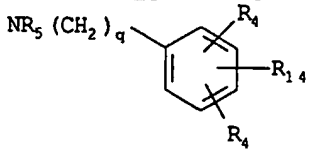
y is 1 to 6;

z is 0 to 6;

or a pharmaceutically acceptable salt thereof;

provided that

when R_3 and R_{18} are hydrogen, R_{20} is not a phenalkylamine of the formula



;

m is 2 when R_{10} is OH in $(CR_{14}R_{14})_n\text{-}C(O)O\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, $(CR_{14}R_{14})_n\text{-}(C(O)NR_{14})\text{-}(CR_{14}R_{14})_m\text{-}R_{10}$, or $C(R_{14}R_{14})_sO\text{-}(CR_{14}R_{14})_mR_{10}$;

when A is N-morpholinyl, N-piperidinyl, N-imidazolyl or N-triazolyl, then q is not 1; and

z is 2-6 in $\text{-}C(R_{14}R_{14})_zR_{10}$ when R_{10} is OH.

The invention further provides for novel pharmaceutical compositions of the compounds of Formula I and a pharmaceutically acceptable excipient.

The invention further provides a method for treating allergic and inflammatory disease which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I).

The invention also provides a method for treating asthma which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

This invention further constitutes a method of inhibiting phosphodiesterase IV in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention further constitutes a method of inhibiting the production of TNF in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of Formula (I).

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically administering an effective amount of a compound of Formula (I).

The compounds of the present invention are also useful in treating additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo.

The compounds of Formula (I) are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo.

Detailed Description of the Invention

All defined alkyl groups can be straight or branched.

Compounds of Formula (I) may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

The term "halogen" is used to mean chloro, fluoro, bromo or iodo. Alkyl groups may be substituted by one or more halogens up to being perhalogenated.

By the term "cycloalkyl" as used herein is meant to include groups of 3-6 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C_{7-11} polycycloalkyl are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo [5.2.1.$0^{2,6}$]decyl, etc., additional examples of which are described in Saccamano et al., WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R_5 and R_{16} in the moiety -NR_5R_{16} together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazoly, 2-triazolyl, tetrazolyl, 2-tetrazoyl, morpholinyl, piperazinyl, or pyrrolyl ring.

The compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and

fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidaozles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B. A preferred disease state for treatment is fungal meningitis.

The preferred organism for treatment is the *Candida* organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

The term "inhibiting the production of TNF" means

a) a decrease of excessive in vivo TNF levels in a human to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages;

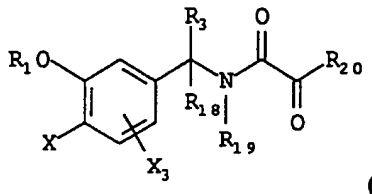
b) a down regulation, at the translational or transcription level, of excessive in vivo TNF levels in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

By the term "TNF mediated disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action is exacerbated or which is secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFβ).

A preferred subgroup of Formula (I) is Formula (Ib):



(Ib)

wherein:

R_1 is phenyl, benzyl or C_{1-2} alkyl unsubstituted or substituted by 1 or more fluorines, C_{4-6} cycloalkyl, CH_2-cyclopentyl, CH_2-cyclopropyl, C_{7-11} polycycloalkyl, 3-tetrahydrofuranyl, cyclopentenyl, $-(CH_2)_nC(O)-O-(CH_2)_mCH_3$, $-(CH_2)_{2-4}OH$, $-(CH_2)_sO(CH_2)_m-CH_3$, $-(CH_2)_n-(C(O)NR_{14})-(CH_2)_m-CH_3$, all of which may be substituted by 1 to 3 methyl groups or one ethyl group;

s is 2 to 4;

m is 0 to 2;

n is 1 to 3;

X is YR_2, halogen, nitro, amine, C_{1-2}dialkylamine, C_{1-2}monoalkylamine or formamide;

Y is O or $S(O)_m$;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 4 fluorines;

R_3 is independently hydrogen, CF_2H, CH_2F, $-CH_2OR_5$, $C(O)OR_5$, $C(O)NR_5R_5$, C(O)H, $C(NOR_5)H$, CH_3, CN, $-C{=}CR_9$ or CF_3;

A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1- or 2-imidazolyl), (2- or 3-thienyl) or (4- or 5-thiazolyl), all of which may be unsubstituted or substituted by one or more: Br, F, Cl, $-NR_5R_6$, NR_5R_{16}, NR_6R_{16}, NO_2, $-COR_7$, $-S(O)_mR_{12}$, CN, OR_5, $-OC(O)NR_5R_{16}$, (1- or 2-imidazolyl), $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)SR_{12}$, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR_{12};

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)SR_{12}$ or $-C(NCN)NR_5R_{16}$;

R_7 is OR_5, NR_5R_{16} or R_5;

R_8 is hydrogen or A;

R_9 is R_5;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl,

piperazinyl or pyrrolyl, and each of these heterocyclic rings is connected at a carbon atom and may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5; or a pharmaceutically acceptable salt thereof;

R_{18} is H, CN, or C_{1-4} alkyl optionally substituted by one or more fluorines;

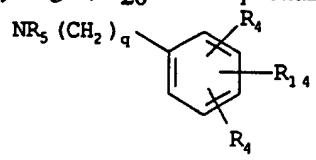
R_{19} is hydrogen, $-(CH_2)_mA$, or $-CH2O(CH2)_mA$;

R_{20} is $O(CH_2)_qR_8$, $-NR_5OR_5$, $NR_5(CH_2)_qR_8$, $-OCH_2NR_5C(O)R_{21}$, and

R_{21} is CH_3 or phenyl;

provided that:

when R_3 and R_{18} are hydrogen, R_{20} is not a phenalkylamine of the formula



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when A is morpholin-4-yl, piperidin-4-yl,imidazol-4-yl, piperidin-4-yl or imidazol-1-yl, then q is not 1.

Preferred compounds are those in which R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, phenyl, tetrahydrofuran-3-yl, 3- or 4-cyclopentenyl, $-C_{1-2}$alkyl optionally substituted by one or more fluorines, $-(CH_2)_nC(O)$-O-$(CH_2)_mCH_3$, $-(CH_2)_sO(CH_2)_m$-CH_3 or $-(CH_2)_{2-4}OH$; X_2 is oxygen; X_3 is hydrogen; X is YR_2 and Y is O; R_2 is a C_{1-2}alkyl optionally substituted by one or more fluorines; R_3 is hydrogen, $C{\equiv}CR_9$, CN, C(O)H, CH_2OH, CH_2F, CF_2H, or CF_3; R_{18} is hydrogen, CN or C_{1-4}alkyl optionally substituted by one or more fluorines; R_{19} is hydrogen or $(CH_2)_mA$; R_{20} is $O(CH_2)_qR_8$, NR_5OR_5, or $NR_5(CH_2)_qR_8$.

More preferred are compounds in which R_1 is C_{1-2} alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl; R_2 is methyl or fluoro substituted C_{1-2} alkyl; R_3 is hydrogen, $C{\equiv}CH$ or CN; and A is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by NR_5R_{16} or $NR_5C(O)R_5$; R_{20} is OR_5, NR_5OR_5 or $NHCH_2A$.

Most preferred are compounds wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CH_3, CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, $C{\equiv}CH$ or CN and is in the 4-position.

Especially preferred are the following compounds:

N-[(3-cyclopentyloxy-4-methoxyphenyl)methyl]oxamide;

Methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate;

N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamic acid;

N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamide;

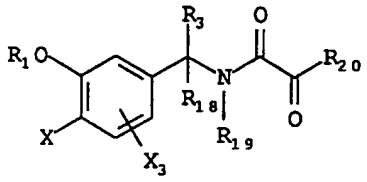
methyl N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate;

N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamide;
and

N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamic acid.

General Synthesis

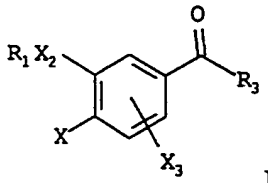
The preparation of compounds of Formula (1) can be carried out by one of skill in the art according to the procedures outlined in the Examples, infra. The preparation of any remaining compounds of Formula (1)



Formula (1)

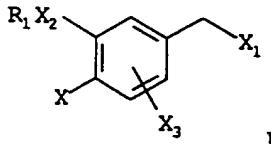
not described therein may be prepared by the analogous processes disclosed herein, which comprises:

a) for compounds of Formula (1) when X and X_3 are other than Br, I, NO_2, or formylamine, and wherein R_1 represents R_1 as defined in relation to a compound of Formula (I) or a group convertible to R_1 and X and X_3 represent X and X_3 as defined in relation to a compound of Formula (I) or a group convertible to X or X_3, begins by reaction of a compound of the Formula (2) when R_3 is H



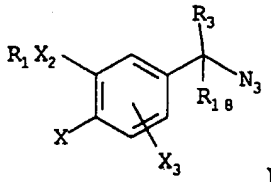
Formula (2)

with a lithium halide and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, to provide a compound of Formula (3) wherein X_1 is halogen.



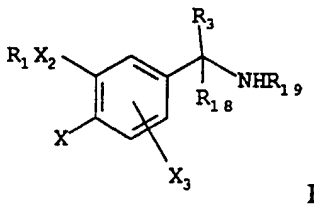
Formula (3)

Halide displacement of a compound of Formula (3) by a metal azide, such as sodium azide in a suitable solvent, such as dimethyl formamide provides a compound of Formula (4)



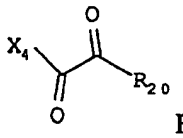
Formula (4)

wherein R_3 and R_{18} are H, which is reduced with an appropriate reductant, such as diimine or hydrogen with a suitable catalyst, such as nickel with ammonia or palladium on carbon with or without an acid to provide a compound of Formula (5) wherein R_{19} is hydrogen.



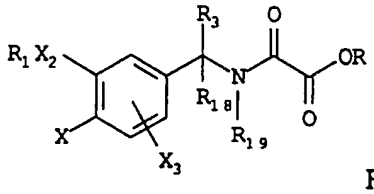
Formula (5)

Compounds of Formula (1) are prepared by reacting a compound of Formula (5) with an appropriately activated oxamic acid derivative of a Formula (6) compound wherein X_4 is an activating group, well known to those skilled in the art, such as those disclosed in Bodansky et al., Peptide Synthesis, Wiley & Sons, publishers (1976) pages 99-109. More preferred X_4 groups are Cl, Br, OCH_2CH_3, $OC(O)CH_3$, $OC(O)CF_3$, O-C(O)-OCH_2CH_3, O-C(O)-$OCH_2CH(CH_3)_2$, or O-C(O)-OCH_2-C_6H_5 in the presence of a non-nucleophilic base.



Formula (6).

Alternatively the R moiety of a Formula (7) compound, a subgroup of Formula (I) may be hydrolyzed



Formula (7)

to R as H, followed by activation of the acid moiety by a halogenating agent, such as an acid halide, oxalyl chloride, or phosphorous oxylchloride, etc.; or a mixed anhydride and reacted with ammonia, an optionally substituted amine, optionally substituted hydroxylamine, or an optionally substituted hydrazine producing the compounds of Formula I wherein R_{20} is R_7R_8, $NR_7NR_7R_8$, NR_7OH, -$NR_5(CH_2)_qR_8$, -$NR_5NR_5R_8$, or -NR_5OR_5.

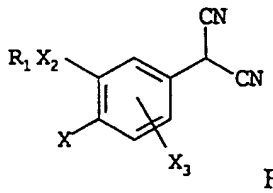
b) or hydrolyzing a compound of Formula (7) as described above, to yield a compound of Formula (7) wherein R is H, and reacting it with ammonia, an optionally substituted amine, optionally substituted hydroxylamine, or an optionally substituted hydrazine and a compound of the formula $R_{22}N=C=NR_{22}$ wherein R_{22} and R_{22} are independently selected from alkyl; cycloalkyl, such as cyclohexyl or dicyclohexyl; alkyl (mono-or dialkyl amino), such as EDAC; aryl or arylalkyl, to produce the compounds of Formula (1) wherein R_{20} is an amine or substituted amine derivative; or

c) for compounds wherein R_3 is not H, and X is substituted with other than Br, I, amino, formylamine, and NO_2, compounds of Formula (4) wherein R_3 and R_8 are H, are allowed to react with a strong hindered base, such as lithium diisopropylamide (LDA) or hexamethyldisilazylithium (LiHMDS) followed by reaction with an electrophilic reagent bearing R_3; conversion of Formula (4) where R_3 is not hydrogen is then accomplished as described above for Formula (4) where R_3 is hydrogen.

A compound of Formula (4) wherein R_3 and R_8 are H; and X is substituted with other than Br, I, amino, formyl amine or NO_2; is reacted with a strong hindered base or a metal hydride and then followed by treatment with an appropriately substituted alkyl halo formate or a dialkylcarbonate to produce the corresponding compound of Formula (4) wherein one of R_3 or R_8 is -CO_2alkyl; or optionally 2 equivalents are used to produce the corresponding disubstituted -CO_2alkyl derivatives of Formula (4); or

A compound of Formula (4) wherein one of R_3 or R_{18} is alkyl and one of R_3 or R_{18} is a -CO_2 alkyl group is produced by reacting the mono-CO_2-alkyl compound produced by the process noted above, with a strong hindered base or a metal hydride followed by treatment with an appropriately substituted alkyl -L wherein L is a leaving group, such as a halide, mesylate or tosylate to produce the desired compound.

Compounds wherein both R_3 and R_{18} are cyano are prepared in an analogous manner using a compound of Formula (8)



Formula (8)

and reacting with a strong hindered base or a metal hydride followed by treatment with an electrophile source of azide, to provide the corresponding compounds of Formula (4) wherein R_3 and R_{18} are CN; the resulting compound may be elaborated to a Formula (1) compound as described above.

Compounds of Formula (1) wherein X or X_3 are formyl amine are formed at the last step, by formylating a compound wherein X or X_3 is NH_2, obtained by removal of a protecting

group from the amine functionality. Such protective groups are well known to those skilled in the art, See Greene, T., supra.

Compounds of Formula (1) wherein X or X_3 are Br or I may be prepared using the techniques of Example 15 on a similarly deprotected amine, diazotization of the amine, and diazonium displacement.

Compounds of Formula (1) wherein X or X_3 are NO_2 may be prepared using the techniques of Example 15 on a similarly deprotected amine by oxidation of the amine to the nitro group.

Compounds of Formula (1) wherein R_3 and R_{18} are other than hydrogen can readily be prepared by one skilled in the art using the techniques illustrated above for R_3 as other than hydrogen.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or via buccal administration. Such formulations are routine in the art.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg to 100 mg/Kg, and preferably from .01 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt therof calculated as the free base. Each dosage unit for intranasal administration or oral inhalation contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 001 to 1.0% of a compound of Formula (I). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably abut 0.001 mg/Kg to 40 mg/Kg, for example abut 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

No unacceptable toxicological effects are expected when these compounds are administered in accordance with the present invention.

The biological activity of the compounds of Formula I as in PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

I. Isolation of PDE Isozymes

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

TABLE 1. Characteristics of PDE isozymes.[a]

Peak	Isozyme	K_m (mM)	
		cAMP	cGMP
1a	cGMP-specific	135	4
Ib	Ca^{2+}/calmodulin-stimulated	50	5
Ic	Ca^{2+}/calmodulin-stimulated	1	2
III	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

[a] Data are from Torphy and Cieslinski, supra.

[b] Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC_{50}s for compounds of this invention range from 25 nM to 500 mM.

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in

intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-100 mM) of PDE inhibitors for one minute and 1 mM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker et al., Radioimmunassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC_{50} for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC_{50}s for compounds of this invention range from 0.3 mM to > 10 mM.

Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

II. In vivo actity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

EXAMPLE 1

3-Cyclopentyloxy-4-methoxybenzaldehyde

3-Cyclopentyloxy-4-methoxybenzaldehyde A mixture of 3-hydroxy-4-methoxybenzaldehyde (40 g, 0.26 mol), potassium carbonate (40 g, 0.29 mol) and bromocyclopentane (32 mL, 0.31 mol) in dimethylformamide (0.25 L) was heated under an argon atmosphere at 100°C. After 4h, additional bromocyclopentane (8.5 mL, 0.08 mol) was added and heating was continued for 4h. The mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure and the residue was partitioned between ether and aqueous sodium bicarbonate. The organic extract was washed with aqueous sodium carbonate and was dried (potassium carbonate). The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 2:1 hexanes/ether to provide a pale yellow oil (52 g, 89%).

Analysis Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.71, H 7.33.

EXAMPLE 2

N-[(3-cyclopentyloxy-4-methoxyphenyl)methylloxamide

2a. α-Bromo-3-cyclopentyloxy-4-methoxytoluene To 3-cyclopentyloxy-4-methoxybenzaldehyde (1.0 g, 4.5 mmol) was added lithium bromide (0.79 g, 9.1 mmol) and acetonitrile (5 mL). Trimethylsilylchloride (0.86 mL, 6.8 mmol) was slowly added and the reaction mixture was stirred at room temperature for 15 min. 1,1,3,3-Tetramethyldisiloxane (1.34 mL, 6.8 mmol) was added dropwise and the resulting mixture was stirred for 3h, diluted with a small amount of acetonitrile, was filtered and the filtrate was separated into two layers. The lower layer was concentrated under reduced pressure, was dissolved in methylene chloride and was refiltered. The solvent was removed *in vacuo* to provide a light tan oil (1.2 g), which was used without further purification.

2b. (3-Cyclopentyloxy-4-methoxyphenyl)methylazide To a solution of a-bromo-3-cyclopentyloxy-4-methoxytoluene (1.2 g) in dimethylformamide (10 mL) under an argon atmosphere was added sodium azide (0.74 g) and the resulting mixture was stirred at room temperature for 20h, was then heated at 100°C for 2h, was cooled, was poured into cold water and was extracted with ether. The organic extract was washed with water and was dried (potassium carbonate). The solvent was removed *in vacuo* to provide a pale yellow oil

.

2c. 2-(3-Cyclopentyloxy-4-methoxyphenyl)methylamine To a solution of (3-cyclopentyloxy-4-methoxyphenyl)-methylazide (0.9 g, 3.6 mmol) in methanol (35 mL) was added 70% perchloric acid (0.4 mL) and 10% palladium on activated carbon (0.3 g). The resulting mixture was hydrogenated at 50 psi hydrogen for 4h and was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The residue was partitioned ether and acidic water, the ether layer was discarded, the aqueous layer was basified with sodium carbonate, was extracted with ether and the ether layer was dried (potassium carbonate). Solvent removal provided an oil.

2d. N-[(3-Cyclopentyloxy-4-methoxyphenyl)methylloxamide A suspension of oxamic acid (0.18 g, 1.98 mmol), N-methylmorpholine (0.22 mL, 1.98 mmol) and ethyl chloroformate (0.19 mL, 1.98 mmol) in ethylene glycol dimethyl ether (8 mL) was stirred at room temperature under an argon atmosphere for 4h. To the suspension was added a solution of 2-(3-cyclopentyloxy-4-methoxy-phenyl)methylamine (0.39 g, 1.28 mmol) in ethylene glycol dimethyl ether (4 mL) and the reaction was stirred for 18h at room temperature. The mixture was partitioned between chloroform and water, the organic layer was washed with dilute hydrochloric acid and was dried (potassium carbonate) and evaporated. Purification by flash chromatography, eluting with 97:3 methylene chloride/methanol, followed by trituration with methylene chloride/ether, provided a solid : m.p.132-135°C.

Analysis Calc. for $C_{15}H_{20}N_2O_4$: C 61.63, H 6.90, N 9.58; found: C 61.76, H 7.10, N 9.31.

EXAMPLE 3

Methyl N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate

3a. 4-Difluoromethoxy-3-hydroxybenzaldehyde A vigorously stirred mixture of 3,4-dihydroxybenzaldehyde (50 g, 362 mmol) and potassium carbonate (50 g, 362 mol) in dimethylformamide (250 mL) was heated under an atmosphere of chlorodifluoromethane using a -78°C condenser at 100°C for 5.5h. An additional quantity of potassium carbonate (10 g) was added and the reaction was continued for another 0.5h. The mixture was allowed to cool, was acidified to pH 5-6 with concentrated hydrochloric acid and was concentrated under reduced pressure. The residue was partitioned between ether and 3N aqueous hydrochloric acid and was extracted five times with ether. The organic extract was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 2:1 hexanes/ethyl acetate, to provide a yellow solid, which was triturated with ethyl acetate/hexanes to provide, in three crops, a white solid : m.p. 84-86°C.

3b. 3-Cyclopropylmethoxy-4-difluoromethoxybenzyl alcohol To a mixture of 3-hydroxy-4-difluoromethoxybenzaldehyde (19.55 g, 104 mmol) and potassium carbonate (21.56 g, 156 mmol) in dimethylformamide (150 mL) under an argon atmosphere at 60°C was added bromomethylcyclopropane (15.13 mL, 156 mmol) and the mixture was stirred and heated at 65°C. After 1.5h, the mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure water was added and the mixture was extracted four times with ethyl acetate. The organic extract was washed twice with water and was dried (sodium sulfate). The solvent was removed in vacuo to provide an oil (26.4 g). This crude aldehyde in absolute ethanol (200 mL) was treated with sodium borohydride (8.23 g, 217 mmol) under an argon atmosphere at room temperature for 20 min. Ten percent aqueous sodium hydroxide (150 mL) was added, the ethanol was removed *in vacuo* and the aqueous residue was extracted three times with ether. The combined organic extract was washed with brine, was dried (sodium sulfate), was filtered and was evaporated to a pale yellow oil (24.38 g, 96% for the two steps).

3c. N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]phthalimide To a solution of 3-cyclopropyl-methoxy-4-difluoromethoxybenzyl alcohol (0.39 g, 1.58 mmol), phthalimide (0.23 g, 1.58 mmol) and triphenylphosphine (0.42 g, 1.58 mmol) in dry tetrahydrofuran (20 mL) under an argon atmosphere was added diethylazodicarboxylate (0.25 mL, 1.58 mmol). The resulting mixture was stirred in the dark overnight and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 25% ethyl acetate/hexanes, to provide a solid : m.p. 71-73°C.

3d. 3-Cyclopropylmethoxy-4-difluoromethoxybenzylamine To a solution of N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]phthalimide (0.5 g, 1.34 mmol) in ethanol (10 mL) under an argon atmosphere was added hydrazine hydrate (0.072 mL, 1.47 mmol). The resulting mixture was heated to reflux for 1h and then was cooled to room temperature. The solids were removed by filtration, the filtrate was acidified to pH 1 with

concentrated hydrochloric acid and was concentrated. The residue was diluted with water and was washed three times with ether and the ether was discarded. The aqueous layer was basified with sodium carbonate and was extracted three times with methylene chloride. The organic layer was dried (potassium carbonate) and evaporated *in vacuo* to provide a clear brown oil.

3e. Methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)methylloxamate

To a solution of 3-cyclopropylmethoxy-4-difluoromethoxybenzylamine (0.15 g, 0.62 mmol) and triethylamine (0.095 mL, 0.68 mmol) in dry tetrahydrofuran (3 mL) at 0°C under an argon atmosphere was added methyl oxalyl chloride (0.057 mL, 0.62 mmol). After 0.5h, the mixture was partitioned between methylene chloride and acidic water, was extracted twice, the organic layer was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 1:1 hexanes/ethyl acetate, to provide an oil.

Analysis Calc. for $C_{15}H_{17}NO_5F_2$: C 54.71, H 5.20, N 4.25; found: C 54.66, H 5.16, N 4.18.

EXAMPLE 4

N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)methylloxamic acid

N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-methylloxamic acid A mixture of methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]-oxamate (0.04 g, 0.12 mmole) and powdered sodium hydroxide (0.015 g. 0.36 mmol) in methanol/tetrahydro-furan/water (5:5:2) under an argon atmosphere was stirred at room temperature for 2h. The reaction mixture was acidified with 3N hydrochloric acid, was diluted with brine and was extracted three times with methylene chloride. The organic extract was dried (magnesium sulfate) and the solvent was removed *in vacuo*. Trituration from the minimal amount of ether/hexanes provided a solid: m.p. 121-123°C.

Analysis Calc. for $C_{14}H_{15}F_2NO_5$: C 53.34, H 4.80, N 4.44; found: C 53.01, H 4.69, N 4.42.

EXAMPLE 5

N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)methylloxamide

N-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-methylloxamide A solution of methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]-oxamate (0.09 g, 0.27 mmole) in methanol (2.5 mL) was cooled to -78°C and anhydrous ammonia (ca. 2 mL) was condensed into the solution. The mixture was allowed to warm to room temperature under stream of argon and the solvent was removed *in vacuo*. The resulting solid was dissolved in ether, was precipitated with hexane and was collected by filtration: m.p. 159-161°C.

Analysis Calc. for $C_{14}H_{16}F_2N_2O_4$: C 53.50, H 5.13, N 8.91; found: C 53.24, H 5.03, N 8.84.

EXAMPLE 6

Methyl N-[1-Cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate

6a. 1-Amino-1-(3-cyclopropylmethoxy-4-difluoromethoxy)-acetonitrile hydrochloride A mixture of 3-cyclopropyl-methoxy-4-difluoromethoxybenzaldehyde (0.8 g, 3.3 mmol) and trimethylsilyl cyanide (0.55 mL, 4.13 mmol) with a trace of anhydrous zinc iodide was stirred at room temperature under an argon atmosphere for 40 min. The mixture was cooled to 0°C, was added to a cold solution of methanolic ammonia (ca. 6.7M, 5 mL), the flask was sealed and the mixture was heated at ca. 40°C for 1.25h. The mixture was allowed to cool, the ammonia was evaporated under a stream of argon, the solvent was removed, the residue was redissolved in methanol and concentrated hydrochloric acid was added. The solvent was removed, the residue was redissolved in methanol, ether was added and the precipitate was collected by filtration and washed with ether: m.p. 165-167°C.

6b. Methyl N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate

To a solution of 1-amino-1-(3-cyclopropylmethoxy-4-difluoromethoxy)acetonitrile hydrochloride (0.175 g, 0.57 mmol) and triethylamine (0.175 mL, 1.25 mmol) in dry methylene chloride (3 mL) at 0°C under an argon atmosphere was added methyl oxalyl chloride (0.057 mL, 0.62 mmol). The mixture was allowed to come to room temperature and after 2h, the mixture was partitioned between methylene chloride and acidic water, the organic layer was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 2:1 hexanes/ethyl acetate, to provide a solid: m.p. 60-62°C.

Analysis Calc. for $C_{16}H_{16}F_2N_2O_5$: C 54.24, H 4.55, N 7.91; found: C 54.18, H 4.57, N 7.70.

EXAMPLE 7

N-[1-Cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamide

N-[1-Cyano-1-(3-Cyclopropylmethoxy-4-difluoro-methoxyphenyl)methyl]oxamide A solution of methyl N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-methyl]oxamate (0.06 g, 0.17 mmole) in methanol (1.5 mL) was cooled to -78°C and anhydrous ammonia (ca. 1 mL) was condensed into the solution. The mixture was allowed to warm to room temperature under stream of argon, was stirred overnight and the solvent was removed *in vacuo*. Purification by flash chromatography, eluting with 1:1 hexanes/ethyl acetate, provided a white solid: m.p. 180-181°C.

Analysis Calc. for $C_{15}H_{15}F_2N_3O_4$: C 53.10, H 4.46, N 12.38; found: C 53.05, H 4.49, N 12.01.

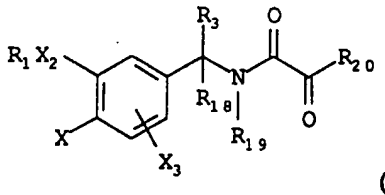
EXAMPLE 8

N-[1-Cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methylloxamic acid

N-[1-Cyano-1-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)methylloxamic acid A mixture of methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]-oxamate (0.15 g, 0.42 mmole), sodium chloride (0.03 g) and water (0.025 mL) in dimethyl sulfoxide (3 mL) under an argon atmosphere was heated at 130°C for 1h. The reaction mixture was cooled and the solvent was evaporated. The mixture was partitioned between ethyl acetate and acidic brine, was extracted three times with ethyl acetate, the extract was dried (magnesium sulfate) and the solvent was removed *in vacuo* to provide a white solid: m.p. >240°C.

CLAIMS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by one or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group, C_{4-6} cycloalkyl containing one or two unsaturated bonds, C_{7-11} polycycloalkyl, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_xOH$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_y$-$R_{11}$, or -$(CR_{14}R_{14})_z$-$R_{10}$;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

Y is O or $S(O)_m$;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -CH_2OR_5, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH{=}CR_9R_9$, -$C{\equiv}CR_9$ or -C(Z)H;

R_4 is independently hydrogen, Br, F, Cl, -NR_5R_{16}, NR_6R_{16}, -NO_2, -$C(Z)R_7$, -$S(O)_mR_{12}$, -CN, OR_5, -$OC(O)NR_5R_{16}$,(1 or 1-(R_5)-2-imidazolyl), -$C(NR_{16})NR_5R_{16}$, -$C(NR_5)SR_{12}$, -$OC(O)R_5$, -$C(NCN)NR_5R_{16}$, -$C(S)NR_5R_{16}$, -$N(R_{16})C(O)R_{15}$, -$NR_{16}C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are NR_5R_{16} they may together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, -$C(O)R_5$, -$C(O)C(O)R_7$, -$C(O)NR_5R_{16}$, -$S(O)_mR_{12}$, -$C(NCN)SR_{12}$, -$C(NCN)R_{12}$, -$C(NR_{16})R_{12}$, -$C(NR_{16})SR_{12}$, or -$C(NCN)NR_5R_{16}$;

R_7 is OR_5, -NR_5R_{16}, or R_{12};

R_8 is hydrogen or A;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted arlyoxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydropyranyl), (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cyclo-alkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5 or when R_5 and R_{16} are NR_5R_6 they may, together with the nitrogen, form a 5 to 7 membered ring optionally containing at least one additional hetero atom selected from O, N or S;;

R_{18} is hydrogen, F, CN, or C_{1-4} alkyl optionally substituted by one or more fluorines, or R_3 and R_{18} together can form a (=O) keto or cyclopropyl moiety;

R_{19} is hydrogen, $-(CH_2)_mA$, or $-CH_2O(CH_2)_mA$;

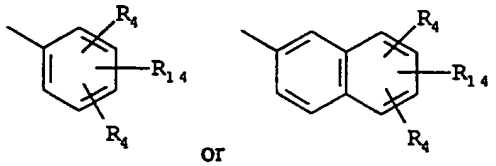
R_{20} is $O(CH_2)_qR_8$, $-NR_5OR_5$, $-NR_5NR_5R_8$, $NR_5(CH_2)_qR_8$, $-OCH_2NR_5C(O)R_{21}$, $-OCH_2C(O)NR_{22}R_{23}$, $-OCH(R_5)OC(O)-C_{1-4}$alkyl, $-OCH(R_5)C(O)OC_{1-3}$alkyl;

R_{21} is CH_3 or phenyl;

R_{22} is hydrogen, CH_3, CH_2CH_3, or CH_2CH_2OH;

R_{23} is hydrogen, CH_3, CH_2CH_3, CH_2CH_2OH, or CH_2CONH_2;

A is C_{1-6}alkyl, (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl), (4 or 5-thiazolyl), triazolyl or quinolinyl, all of which may be unsubstituted or substituted by one or more R_4 groups; or A is $-(CH_2)_rSR_{12}$; or A is (a) or (b)



(a) (b)

where the R_4 and R_{14} groups are at any open position on the naphthyl ring;

Z is O, NR_{12}, NOR_5, NCN, $C(\text{-CN})_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, $C(\text{-CN})NO_2$, $C(\text{-CN})C(O)OR_{12}$ or $C(\text{-CN})C(O)NR_5R_5$;

m is 0 to 2;

n is 1 to 4;

q is 0 to 1;

r is 1 to 2;

s is 2 to 4;

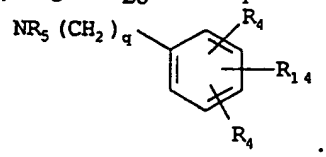
x is 2 to 6;

y is 1 to 6;

z is 0 to 6;

provided that;

when R_3 and R_{18} are hydrogen, R_{20} is not a phenalkylamine of the formula



;

m is 2 when R_{10} is OH in $(CR_{14}R_{14})_n$-C(O)O-$(CR_{14}R_{14})_m$-R_{10}, $(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-R_{10}, or $C(R_{14}R_{14})_s$O-$(CR_{14}R_{14})_m R_{10}$;

when A is N-morpholinyl, N-piperidinyl, N-imidazolyl or N-triazolyl, then q is not 1; and

z is 2-6 in -$C(R_{14}R_{14})_z R_{10}$ when R_{10} is OH.

2. A compound of claim 1 wherein R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, phenyl, tetrahydrofuran-3-yl, 3- or 4-cyclopentenyl, -C_{1-2}alkyl optionally substituted by one or more fluorines, -$(CH_2)_n C(O)$-O-$(CH_2)_m CH_3$, -$(CH_2)_s O(CH_2)_m$-CH_3 or -$(CH_2)_{2-4}$OH; X_2 is oxygen; X_3 is hydrogen; X is YR_2 and Y is O; R_2 is a C_{1-2}alkyl optionally substituted by one or more fluorines; R_3 is hydrogen, C≡CR_9, CN, C(O)H, CH_2OH, CH_2F, CF_2H, or CF_3; R_{18} is hydrogen, CN or C_{1-4} alkyl optionally substituted byone or more fluorines; R_{19} is hydrogen or $(CH_2)_m$A; R_{20} is $O(CH_2)_q R_8$, NR_5OR_5, or $NR_5(CH_2)_q R_8$.

3. A compound of claim 2 wherein R_1 is C_{1-2} alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl; R_2 is methyl or fluoro substituted C_{1-2} alkyl; R_3 is hydrogen, C≡CH or CN; and A is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by NR_5R_{16} or $NR_5C(O)R_5$; R_{20} is OR_5, NR_5OR_5 or $NHCH_2A$.

4. A compound of claim 3 wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CH_3, CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, C≡CH or CN and is in the 4-position.

5. A compound of claim 1 selected from the group consisting of:

N-[(3-cyclopentyloxy-4-methoxyphenyl)methyl]oxamide;

methyl N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate;

N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamic acid;

N-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamide;

Methyl N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamate;

N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamide; and

N-[1-cyano-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)methyl]oxamic acid.

6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

7. A method of treating allergic and inflammatory diseases which comprise administering to a subject in need thereof, an effective amount of a compound of claim 1.

8. A method of treating asthma which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00552

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 237/22; A61K 31/16
US CL :564/158;541/616
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/158;541/616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A, 92/00968 (Bender et al.) 23 January 1992, see entire document.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 18 MARCH 1993	Date of mailing of the international search report 25 MAR 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer SCOTT RAND Telephone No. (703) 305-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00552

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application claims which do not relate to one invention so as to form a single invention concept. Thus, there is lack of unity under PCT Rule 13.

Compounds, compositions, and methods of treating allergy, asthma, or inflammation wherein the species comprises:

I. Oxamate compounds wherein R_3 is cyano, such as example 6, classified in class 558/407 and 514/521 for example (claims 1-8, in part).

II. Oxamic and compounds wherein R_3 is cyano, such as Example 8, classified in class 558/407 and 514/521, for example (claims 1-8, in part).

III. Oxamides wherein R_3 is cyano, such as Example 7, classified in class 588/404 and 514/521, for example (claims 1-8, in part).

IV. Oxamate compounds not provided for above, such as Example 3, classified in class 560/39 and 514/563 for example (claims 1-8, in part).

V. Oxamic acid compounds not provided for above, such as Example 4, classified in class 562/444 and 514/563, for example (claims 1-8, in part).

VI. Oxamides not provided for above, such as Examples 2 and 5, classified in class 564/158 and 514/616.

Groups I-VI do not fulfill the requirement for unity of invention under Rule 13.2 because the various species are so diverse so as to lack a special technical feature in common.